REMARKS

Claims 1, 4, 7, and 18-26 are pending in the application. No amendments have been made by the present response.

Finality of the Office Action Dated May 26, 2006

In the response to the final Office Action dated May 26, 2006, applicants contested the finality of the action (asserting that the claim amendments did not necessitate the new grounds of rejection). After further discussions with Examiners Wood and Tate on this issue, no agreement was reached and the finality of that action has not been withdrawn. However, Examiner Tate stated in a telephone conference with the undersigned on June 25, 2007 that should the Office decide to issue another action on the merits for this application, that action will be made non-final. Applicants appreciate the Examiners' helpful discussions on this issue.

35 U.S.C. § 103(a) (Obviousness)

At pages 2-5 of the final Office Action dated May 26, 2006, claims 1, 4, 7, and 18-26 were finally rejected as allegedly unpatentable over Birnbaumer et al., U.S. Patent No. 5,932,417 ("Birnbaumer") in view of Draznin et al. (1987) J. Biol. Chem. 262(30):14385-88 ("Draznin") and further in view of Bruton et al. (2001) Acta Physiol. Scand. 171:259-65 ("Bruton").

Applicants respectfully traverse the rejection in view of the following remarks.

The currently claimed invention is based, at least in part, upon the inventors' surprising discovery that inhibition of "store-mediated" Ca^{2+} entry (SMCE) results in a decrease in insulin-stimulated glucose uptake in skeletal muscle. This finding supports a physiological role of SMCE and Ca^{2+} alterations in insulin action in skeletal muscle, where an increase in Ca^{2+} entry results in an increased insulin-mediated glucose uptake.

Consistent with the inventors' discovery, the claims are directed to methods for identifying compounds that increase SMCE as agents that increase cellular glucose uptake. Each of independent claims 1, 4, and 7 contains a step of determining whether an agent that increases SMCE (or stimulates a function of a SMCE regulating factor) increases glucose uptake in a cell.

Birnbaumer, the primary reference cited in the present obviousness rejection, describes human "transient receptor potential" (trp) proteins and methods of treating cells with a trp-

control agent to raise or lower the amount of biologically active trp protein and thereby control capacitative calcium ion entry into the cell. Birnbaumer's only disclosure related to insulin or diabetes is as follows: "Examples of treatment protocols in accordance with the present invention involving the use of trp control agents to control calcium ion levels are as follows ... stimulation of pancreatic β-cell CCE to stimulate insulin secretion in type II (non-insulin-dependent) diabetes." (Birnbaumer at column 15, lines 30-40).

The above-cited passage from Birnbaumer indicates that stimulation of CCE in β-cells can stimulate insulin secretion in type II diabetes. However, neither this passage nor any other in Birnbaumer suggests that stimulating CCE in a cell will trigger an increase in glucose uptake in that cell. Stimulation of insulin secretion from β-cells (as described by Birnbaumer) is a biological phenomenon distinct from stimulation of glucose uptake in a cell (e.g., a muscle cell). Any suggestion by Birnbaumer that CCE stimulation in β-cells will cause an increase in their secretion of insulin provides no suggestion whatsoever that stimulating CCE in a cell will increase glucose uptake in that cell. As noted above, all of the pending claims contain a step of determining whether an agent that increases SMCE (or stimulates a function of a SMCE regulating factor) increases glucose uptake in a cell.

Neither Draznin nor Bruton, the secondary references cited in the present rejection, cures the above-noted deficiencies of Birnbaumer. As detailed below, nothing in these secondary references (taken alone or in combination) suggests that stimulation of SMCE in a cell will result in increased glucose uptake in that cell.

Draznin discloses that an optimal concentration of intracellular Ca^{2+} exists in adipocytes at which insulin-mediated glucose uptake can occur and that increased Ca^{2+} diminishes insulin-stimulated glucose uptake (Draznin at Abstract and page 14386). Draznin states that its observations "strongly suggest that high $[Ca^{2+}]_i$ may be a mechanism for deactivation or possibly termination of insulin action" (Draznin at page 14388, left column). In its conclusion, Draznin states that "[i]n obesity or in normal subjects receiving glucose/insulin infusions, increasing intracellular Ca^{2+} may result in overt insulin resistance" (Draznin at page 14388, right column).

The foregoing passages from Draznin (i) do not describe or suggest a role for SMCE in insulin-stimulated glucose uptake (Draznin does not suggest that the experimental findings described therein occur via SMCE), and (ii) indicate that increased intracellular calcium

concentration diminishes insulin-stimulated glucose uptake and may trigger insulin resistance. In view of its experimental findings and conclusions regarding the negative effects of high calcium concentration on insulin-stimulated glucose uptake, the teachings of Draznin would not have led the skilled person to evaluate compounds that stimulate SMCE for their ability to increase cellular glucose uptake. In fact, Draznin teaches away from the currently claimed methods insofar as it states that increased calcium concentration diminishes insulin-stimulated glucose uptake and may trigger insulin resistance.

Bruton reviews several references that describe possible roles for calcium and calmodulin in insulin signaling in mammalian skeletal muscle. However, nothing in Bruton suggests that SMCE is involved in insulin-stimulated glucose uptake in skeletal muscle. The claimed invention relates to SMCE as a stimulator of glucose uptake and is supported in part by the inventors' discovery that application of SMCE inhibitors to skeletal muscle caused a dose-dependent decrease insulin-stimulated glucose uptake. Bruton does not report any experimental findings describing an effect of SMCE stimulators or inhibitors on glucose uptake. Furthermore, Bruton's review of Cartree's studies with L-type calcium channel inhibitors (such as nifedipine) provides no suggestion that SMCE inhibitors would cause a decrease in insulin-stimulated glucose uptake. The effect of SMCE inhibitors on glucose uptake was discovered by the inventors and was not suggested by the references described in Bruton.

In view of the foregoing, applicants respectfully submit that the cited references do not suggest that increasing SMCE in a cell will result in an increase in glucose uptake in the cell. As a result, the references do not render obvious independent claims 1, 4, or 7 or the claims that depend therefrom. Applicants request that the Examiner withdraw the rejection.

CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are now in condition for allowance, which action is requested.

Enclosed is a Petition for Extension of Time. The extension of time fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges (or credits) to deposit account 06-1050, referencing Attorney Docket No. 13425-115001.

Respectfully submitted,

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